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BLEEDING IN TYPHOID FEVER.

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It is generally recognized that the occurrence of hemorrhage in the course of typhoid fever is a serious matter, especially when it appears late in the disease. The degree of seriousness of this complication, however, has been differently estimated by writers, and one finds Trousseau and Graves constantly quoted as declaring that it was not an unfavorable event and sometimes even of advantage, while Murchison, Dieulafoy,[1] and others state that it is a bad omen and not even of transient benefit. Thus, on the one hand, Leibermeister[2] writes: "If at the end of the third or fourth week a large intestinal hemorrhage appears, it may occur that the marked fall of temperature with it will have a favorable influence upon the enteric phenomena present, recovery steadily advancing from that time on. These are the cases that have led competent observers (Graves, Trousseau) to maintain that intestinal hemorrhages are by no means unfavorable in enteric fever, but are rather of favorable prognostic import." On the other hand, Murchison wrote: "Although I have seen patients recover after a profuse hemorrhage, I have never seen the slightest benefit from it."[3]

It is admitted by every writer that the temperature often tends to fall after a hemorrhage, but most state that along with this lessening in the temperature there is a rise in the rate of the pulse. Thus, for example, Curschmann[4] says: "In those cases in which the patient does not die during the first copious hemorrhage the clinical picture becomes alarmingly altered. The skin acquires a waxy pallor, there is relaxation of the features, the pulse becomes small and shows greatly increased frequency, lividity and coldness of the extremities and possibly syncope appear. With the rapid increase in the pulse frequency there is generally associated a rapid reduction in the bodily temperature. The curve may be observed to decline from 40° or 41° C. to far below the normal—to 35° C. and below—in a few hours. This characteristic intersection of the pulse and temperature curves is of grave prognosis." He adds later, "Quite rarely I have seen the pulse-frequency fall parallel with the temperature curve—a condition that is without doubt to be considered as a favorable prognostic sign." Again, T. McCrae,[5] in speaking of hemorrhage in typhoid fever, says: "The temperature usually falls, and the drop may be as much as 10° and to below normal. Still, even a sharp hemorrhage may have no effect on the temperature. The pulse-rate rises, and with it the quality alters. At first somewhat bounding, later it becomes small and somewhat running." He also says later: "That results of hemorrhage are very various, and there is no doubt that some patients do seem to be benefited. These are usually robust and but slightly toxic. The temperature curve may be lower, the pulse not increased in rate or even decreased, and the whole character of the attack milder." One can easily realize that if the hemorrhage be very profuse a state of shock will ensue, with a marked fall in the temperature and rise in the rate of the pulse, along with all the other signs of an acute and profound anemia; but the rule seems to be, certainly in our series, that the temperature and pulse-rate fall together, with, as will be shown, a frequent improvement in the general condition of the sufferer.

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[1] Text-book of Medicine (translation), ii, 1026.

[2] Modern Clinical Methods in Infectious Diseases, p. 30; The Physiology of Blood-letting, British Med. Jour., 1910, i, 104.

[3] Sir Thomas Watson, Principles and Practice of Medicine, ii, 881.

[4] Typhoid and Typhus Fevers, Nothnagel's Encyclopedia of Practical Medicine, p. 223.

It is difficult to believe that two such keen observers as Trousseau and Graves could have meant that bleeding in typhoid fever was not a serious thing, and probably Flagge was right when he wrote,[6] "Probably the real basis of their opinion was the fact that a good many patients recover from it, or, in other words, that it was not so often directly fatal as might have been anticipated." Certainly any statistical study of the disease makes it evident that the cases which have had hemorrhages have a much higher death rate than have others not so complicated. Thus in studying the last 1591 cases of typhoid fever treated in the Toronto General Hospital it appears that the mortality was 8.67 per cent. over all, but that the death-rate among those reported as having had one or more hemorrhages was 37 per cent. This latter figure is almost the same as occurred in Cruschmann's series at Leipsic, which was 38 per cent.,[7] while in Strümpell's forty-five cases of hemorrhage in typhoid fever it was 42.2 per cent. In our series, if we exclude the cases that had bleeding, we find that the mortality of the remaining 1464 cases was only 6.3 per cent.

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[5] Osler's Modern Medicine, i, 127.

[6] J. Hilton Fagge, Principles and Practice of Medicine, i, 170 and 180.

[7] Osler's Modern Medicine, p. 127.

The question here arises as to why enteric fever complicated with hemorrhage should have such a higher death-rate. The ill-effects of bleeding may be due (1) to the actual loss of blood, which may be directly fatal (as it was in eight out of Strümpell's nineteen deaths in typhoid complicated with hemorrhage), or the anemia may so weaken the patient as to lay him open to other complication, or (2) the bleeding may denote perforation, and in any case is usually significant of a severe infection. If it were not for these two classes of dangers, which are more or less imminent in hemorrhage cases, the loss of blood, if of moderate amount, might be welcome. Many writers, for example Leibermeister and McCrae, not to mention Trousseau and Graves, have remarked how often patients seem to improve after moderate hemorrhages, and if it were not for the dangers looming up of the bleeding becoming uncontrollable or being a precursor of perforation, probably most physicians would be pleased rather than otherwise with the at least temporary benefit which so often accrues.

The appended twelve charts are taken from among the cases of intestinal hemorrhage (with one exception where the bleeding was through venesection) that occurred in our series at the Toronto General Hospital, and they show how the bleeding was followed by a more or less marked fall not only in the temperature but also in the pulse rate. They are perhaps the best examples, but most of the other one hundred and fifteen charts of cases with bleeding showed more or less of the same thing. They do not, of course, show the improvement in the general condition that was so often noted, but a perusal of the epitomes of the histories will make this evident. The notes of progress are exactly as they were made at the time by members of the staff and the house physicians. It will be noted that the improvement in the temperature and pulse curves, while often transient, in some cases may last for days and may even usher in convalescence. It is impossible in the face of such evidence to agree with Fagge when he says: "According to Liebermeister, hemorrhage also diminishes the pulse, and is often attended by a marked amelioration of the cerebral symptoms. But all these effects are transitory, for by the end of twenty-four hours the fever is as high or higher than before the hemorrhage." Or with Murchison, who wrote: "I have seen patients recover from profuse hemorrhages. I have never seen the slightest benefit from it."

It is difficult to explain how the good effects that may follow a hemorrhage come about. There is no doubt, however, but that it produces a profound effect upon the whole bodily economy. Thus bleeding has been shown to bring about an increase in the flow to urine;[8] to greatly increase the intake of oxygen, with proportionate raising of tissue-oxidation.[9] It hastens the coagulation time of the blood more than does any other single agent with which we are acquainted.[10] Roux and Vaillard showed in 1893 that it produced a rapid increase in the antibodies contained in the blood, and Dreyer and Schroeder, of Copenhagen, about four years ago, demonstrated that it increases the specific antibodies in typhoid and paratyphoid, both in experimental animals and in man. H. Whitehead[11] fully confirmed this two years ago in a study of typhoid complicated by hemorrhage, in which the agglutinating power of the blood was enormously raised by the bleeding. Further, in toxic conditions, such as uremia and other less-defined states, states, where there is high blood pressure, bleeding appears to in some way lessen the toxemia, and possibly in typhoid it may have some similar effect.

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[8] Potochi, Revue Pratique d'Obstétrique et de Gynécologie, January 20, 1911, No. 1, p. 28.

Finally, Whitehead, in his paper two years ago, suggested that the good effects of hemorrhage in typhoid fever might be attained and the evil ones (associated with intestinal hemorrhage) avoided by the timely use of venesection in those cases which are not doing well on account of severe infection and toxemia, and with this suggestion I heartily concur. Of course, in the days when venesection was considered to be a panacea for almost all ailments, cases of typhoid fever must have been bled, but it is impossible to get at any reliable data as to the results, as at that date typhoid fever was not differentiated from other cases of continued fever. Even Marshall Hall, who is considered to be the great opponent of bleeding, and who is given the credit of having brought about the almost complete abandoment of this time-honored method of treatment, states that in severe and eruptive fevers[12] from six to fourteen ounces of blood should be removed, so that it is not likely that cases of typhoid fever escaped.

So far only one case can be shown in our series (Case VII), but the sequence of the venesection was there most marked. Theoretically the method appears to be indicated in severe cases and if the removal of blood by venesection be a moderate one, say of six to fourteen ounces, as was recommended by Marshall Hall, it can do no harm and may possibly be productive of great good.

EPITOME OF CASES.

CASE 1 (Not yet filed).—Female, aged twenty-two years. Admitted October 1, 1911. Duration of illness, about two weeks. Was dull and drowsy; flushed.

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[9] Beaumont Small, Reference Handbook of the Medical Sciences, ii, 71.

[10] Rudolf and Cole, The Coagulation Time of the Blood in Various Diseases, AMER. JOUR. MED. SCI., October, 1911.

[11] Intestinal Hemorrhage in Typhoid Fever, Lancet, 1911, ii, 1067.

[12] Marshall Hall, The Cyclopedia of Practical Medicine, 1833, quoted by D'Arcy Power, Practitioner, 1909.

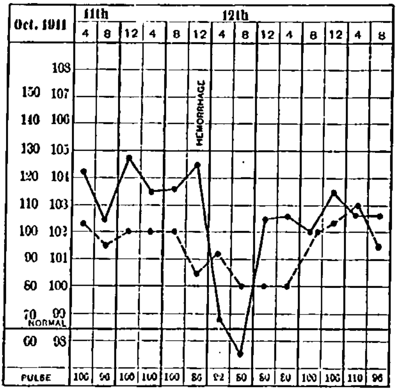
October 7. Vomited a great deal, and was dull and very toxic.

October 12. Very dull and toxic. Vomited twice. At 5.30 A.M. there was a profuse hemorrhage from bowel.

October 13. Brighter. Pulse, 92. Temperature, 98.6. Systolic blood pressure, 72; diastolic, 45.

October 19. Brighter. Toxemia not so marked. Temperature, 102.4°; pulse, 92; respiration, 22.

October 31. Quiet; sleeping well. No vomiting since October 12. Steadily improved, and was discharged well on January 21, 1912.



CASE I

CASE II (Vol. xxxix, Case 6088).—Male, aged thirty-five years. Admitted October 4, 1909. Duration of illness, about two weeks. Was in fairly good condition. Abdomen not distended; pulse very dicrotic.

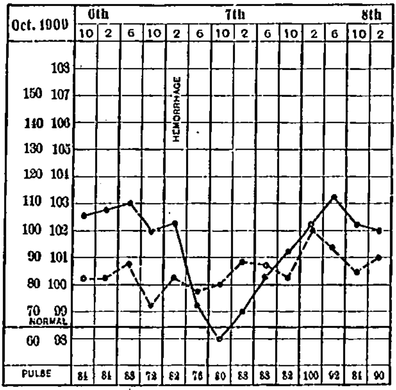
October 6. Chilly and free sweats. Lips dry. Tongue clean and red. Later in the day was drowsy and had severe headache and abdominal distress.

October 7. In early morning and again just before noon the patient complained of chilly feelings, and sweated. Was quite restless, and had severe abdominal pain, with no rigidity or tenderness. Some nausea. Bowel movement at noon showed small amount of dark blood. Half an hour later a large amount of blood. Pulse not changed. An hour later a third hemorrhage—very large. No change in pulse until then, when it became rapid, and he had a general faint feeling, blanched and hands clammy, and half an hour later had a profuse perspiration. At midnight the pulse-rate was not changed; temperature, 99°.

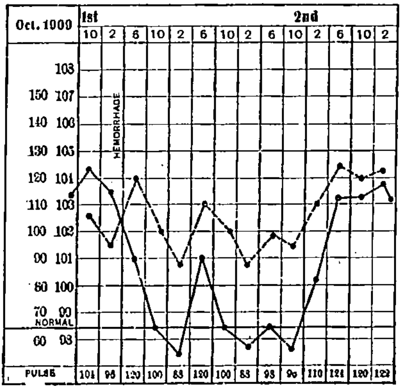
October 8. Slight hemorrhage at 9 A.M. This recurred slightly for two days. Pulse-rate not altered for the worse.

October 11. General condition satisfactory. Temperature running at a satisfactory height.

November 13. Uninterrupted progress. Soon after he left the hospital well.



CASE II



CASE III

Case III (Vol. xlvii, Case 6917).—Female, aged twenty-eight years. Admitted September 19, 1909. Duration of illness, about one month. Fairly severe attack.

September 26. Very drowsy and slept most of the day. Tongue drying. Some diarrhea (5). Abdomen distended.

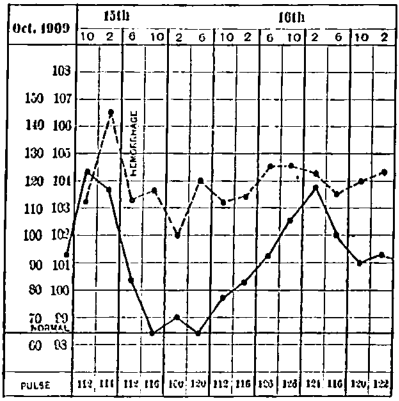
September 29. Abdomen distention marked. Pulse dicrotic. Patient very dull.

October 1. Hemorrhage occurred in night and today several times. Pallid. Skin cold and clammy. Pulse of poor quality. Respiration sighing.

October 2. No more hemorrhage. Patient brighter.

October 4. Abdomen distended. Respiration sighing. Pallor marked but pulse unchanged. Resting well at night.

October 5. Slight hemorrhage today. This patient eventually left the hospital well.



Case IV.

Case IV (Vol. xlvii, Case 6926).—Male, aged thirty years. Admitted September 30, 1909. Duration, five days. Severe case, with high fever, easily lowered always by three grains of aspirin.

October 14. Has a restless night; tried to get out of bed, and talked to himself. Subsultus marked. Sweated freely. Very drowsy, but rational until tonight; sitting up in bed and trying to get out of it. 8 p.m.: pulse 120; respiration, 20; temperature, 105°, 10 p.m.: pulse, 104; respiration, 20; temperature, 100.2°. Pulse and abdomen good.

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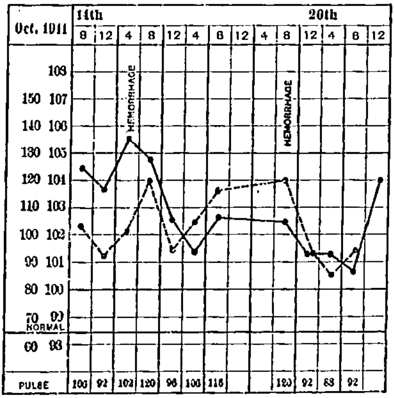
October 15. Profuse hemorrhage at 6 A.M., which was bright red. Pulse irregular and intermittent, small and thready. Profuse sweating. 8 A.M.: pulse, 144; respiration, 32; temperature, 103.2°. At noon patient was quite bright; pulse, 112; respiration, 24; temperature., 100.2°. 4 P.M.: pulse 116; respiration, 28; temperature, 98.2°. 8 P.M.: pulse, 120; respiration, 20; temperature, 99°. Pulse of better quality. Another hemorrhage in evening. Midnight: pulse, 120; respiration, 20; temperature, 98.3°.

October 16. Noon: pulse, 120; respiration, 24; temperature, 101.1°. Patient brighter. Pulse of better quality than in morning. Patient very quiet; slept most of the day. Abdomen and pulse satisfactory. After this the patient had a number of hemorrhages at intervals of several days. Each one was followed by a temporary drop in temperature and pulse-rate and an improvement in general condition. He eventually completely recovered.



CASE V

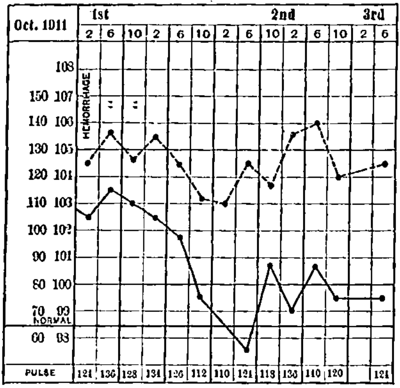
CASE V (Vol. lxxiv, Case 9772).—Male, aged twenty-six years. Admitted October 9, 1911. Duration of illness, ten days. Dull and heavy, and covered with rose spots. Lips dry. Temperature, 104.8°.

October 14. Very dull and heavy. Perspiring freely. Respiration, 36; pulse, 105. Had a free hemorrhage this morning.

October 15. Patient appears to be improved; less toxic. Tongue very dry.

October 16. Pale and hard to arouse. Had two hemorrhages. Twitching of eyebrows and mouth. Tongue very dry.

October 17. Brighter and better in every way. After this he steadily improved, and left the hospital well on December 21.



Case VI

Case VI (Vol. lxxiv, Case 9773).—Female, aged fourteen years. Admitted September 13, 1911. Duration of illness, about twenty-six days. Very ill on admission. Tongue pale and moist, and covered with white fur. Abdomen distended. Remained ill and toxic during the next few days.

September 30. Had a restless night. Temperature, 103° to 104°; pulse, 124.

October 1. No marked abdominal distention. At 11 p.m. had rather profuse hemorrhage and again next day.

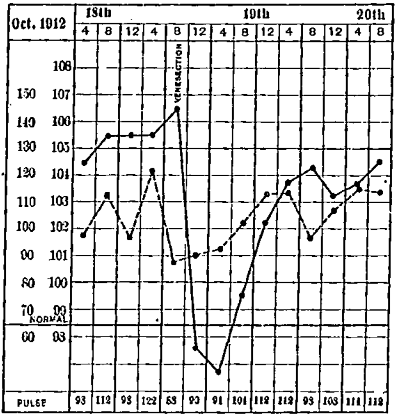
October 2. Abdomen distended. Involuntary urine. Later became worse and more toxic, with filling up of bases of lungs, and died October 5.

Case VII (Not yet filed.).—Female, aged thirty-four years. Admitted October 17, 1912. Duration of illness, two weeks. Very toxic and paid no attention to surroundings. Lips dry and cracked. Tongue reddish brown. Spasmodic movement of chin. Hands tremulous. Abdomen distended and tympanitic. Spleen and liver palpable.

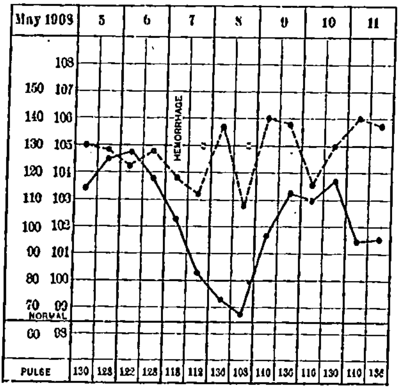
October 18. About the same. Seemed dazed, and at times picked at bedclothing. Temperature, 105°; pulse, 110. In the evening five ounces of blood were drawn off from median basilic vein of left arm and ten ounces of normal saline solution were injected into the vein. 6 p.m.: temperature, 106°; pulse, 130. Whisky, half an ounce, every four hours. Cold colon douche. Ice pack. Caffeine gr. 1, aspirin gr. 2, and acetanilide gr. ½, to be repeated in half an hour, and again in two hours if temperature did not lower.

October 19. 9 A.M.: temperature, 99°; pulse, 88. Listless and weak. Muttered at times. Tongue dry and reddish brown. Lips dry. After this she continued very ill, but less desperately so, and by the end of the month was much better and left the hospital well before the end of the year.

CASE VIII (Vol. xxv, Case 4210).—Female, aged thirty-two years. Admitted April 28, 1908. Duration, ten days. Was very ill on admission.



CASE VII



CASE VIII

May 1. Temperature high. Delirious and weak.

May 7. Hemorrhages early in morning and again at 1 P.M. Blood dark and not in large quantity. Abdomen much distended.

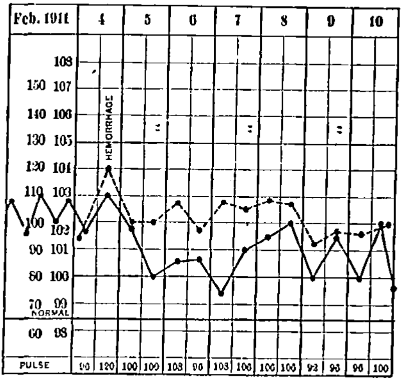
May 8. Another hemorrhage (slight) at 11.30. Distention still marked. A free hemorrhage at 6.15 P.M. Pulse much as before.

May 10. Pulse weak. Restless and unconscious most of time.

May 13. Marked improvement in last two days.

May 19. Weaker, and died at 5.15 A.M.

CASE IX (Vol. lxiii, Case 8870.).—Male, aged thirty-one years. Admitted January 19, 1911. Duration of illness, about nine days. Fairly well on admission. Was evidently near the end of the attack. Temperature, 100°, and was soon normal. A week later had a relapse, and on February 4 a hemorrhage. On day before was dull and sleepy. Systolic blood pressure, 110. Slight bloating. Lips crusted and tongue red and beefy. Had another hemorrhage on February 5 and again on February 7 and 9. After that the patient steadily improved and left the hospital well on March 25.



CASE IX

CASE X (Vol. xxxi, Case 5145).—Male, aged twenty-two years. Admitted October 22, 1908. Had been ill for two weeks. Weak; sleepy; delirious; hard to arouse.

October 28. Had a hemorrhage.

October 30. Had a hemorrhage.

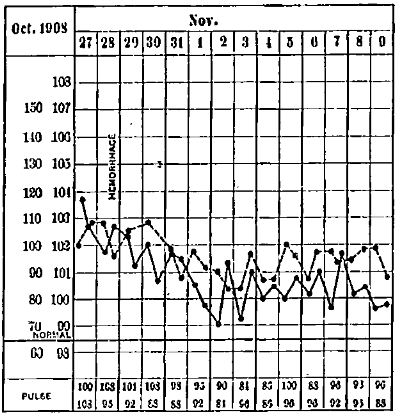
November 1. Not so delirious; taking nourishment well.

November 4. Able to speak. Recovered without further complications.

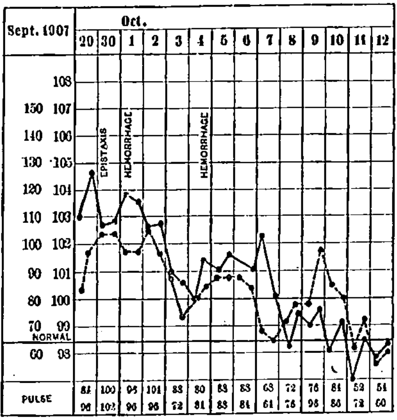
CASE XI (Vol. xviii, Case 3302).—Male, aged twenty-two years. Admitted September 23, 1907. Had been ill for three weeks when admitted; feeling better. Pulse showed marked dicrotism.

September 30. Epistaxis; feeling better.

October 1. Slight hemorrhage from bowel. Pulse and temperature not affected by it.



Case X



Case XI

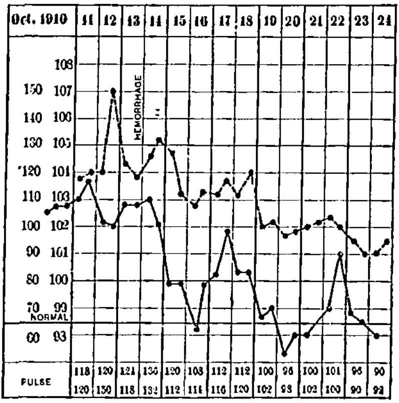
October 4. Another slight hemorrhage.

October 5. Systolic blood pressure, 120.

October 10. Another epistaxis. Feeling well.

November 2. Discharged well.

CASE XII (Vol. lxiii, Case 8691).—Male, aged twenty-four years. Admitted September 19, 1910. Had been ill for four weeks. Very ill and drowsy; pallid; tongue dry and coated.



CASE XII

October 11. Nervous and trembling; very toxic; involuntary evacuations. Looked almost moribund. Drowsy and stupid. Lungs showed a consolidation at the right base. Extremely ill.

October 13. Very ill; profuse hemorrhage today.

October 14. More clots in stools.

October 15. Much better. Lung condition clearing. Pulse, 106 to 122; temperature, 98.2° to 99.2°. Had a good day, but did not rest so well during the night.

November 3. Doing well. Temperature and pulse normal. Was discharged well on November 27.

RECONSIDERATION OF THE QUESTION OF EXPERIMENTAL HYPERTROPHY OF THE THYROID GLAND, AND THE EFFECT OF EXCISION OF THIS ORGAN UPON OTHER OF THE DUCTLESS GLANDS.[1]

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THE space allotted is so short that I cannot do more than indicate in merest outline a few of the problems which have presented themselves in the course of our study in animals and the human subject of the functions of some of the glands of internal secretion.

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[1] Read, by invitation, May 7, 1913, before the Association of American Physicians at the Ninth Triennial Session of the Congress of American Physicians and Surgeons.

Twenty-five years ago, in the course of experiments upon the dog, undertaken chiefly with a view of determining the cause of death after operations upon the thyroid gland, I was surprised to find that excisions or transplantations or simple manipulations of the thyroid lobe were, after a time and almost invariably, followed by increase in the size of the remaining portions of the gland, wherever situated.

Examination of the hypertrophied tissue revealed the most unexpected and astonishing histological picture, a structure so different from the normal gland that not one of the several eminent pathologists in this country and abroad, to whom I showed the sections, was able to identify it. The histological changes which resemble those found in exophthalmic goitre are now so well known as not to require mention at this time. With few exceptions this hypertrophic picture made its appearance within twenty-two days after operation of any kind upon the thyroid gland, and even in its most advanced type was observed so late as ninety-five days after operation.

My observations have been confirmed by many, most carefully and convincingly by Marine, and the hypertrophy has generally been regarded as compensatory.

In my original article I expressed the view that possibly some form of auto-intoxication might account for the hypertrophic changes, and for some years have thought that the hyperplasia of the remaining thyroid tissue which has followed excision of a portion of the gland might possibly be due to infection of the wound, and for the following reasons:

1. The increase in the size of the remaining thyroids and the degree of hyperplasia as indicated by the histological picture seemed to bear no relation to the amount removed. The excision of so little as one-fourth of one lobe might be followed by great increase in the size of both lobes, and by the histological changes which characterize hyperplasia.

2. In 1888 I found that hypertrophy of the thyroid glands of dogs occurred after the injection of several cubic centimeters of a bouillon culture of Staphylococcus aureus into the peritoneal cavity, and also when a mild form of peritonitis had been produced in these animals—a peritonitis which was not rapidly fatal.

3. Experiments conducted in 1906 and 1907, in the Hunterian Laboratory, seemed to indicate that for the successful transplantation of a parathyroid glandule a considerable deficiency must be created.

4. Twice in the course of the past five years I have had opportunity to examine the remaining lobe of the thyroid gland after

excision of the other in dogs whose wounds had healed throughout without suppuration, and have noted that there was no hyperplasia of the former.

5. From a restudy of the report of my experiments on extirpation of the thyroid gland made in 1888, I find that for the major part of the experiments the wounds of the dogs were left open, and that after twenty-two days, with few exceptions, there was hypertrophy, macroscopic and microscopic, of the remaining gland in the animals whose wounds were permitted to heal by granulation, whereas when the wound healed *per primam* the hyperplasia of the remaining thyroid tissue developed perhaps less regularly and not to the same extent.

6. Manifestations of hyperthyroidism may develop promptly after tonsillitis, appendicitis, pneumonia, typhoid fever, and other infections.

In October, 1912, I proposed to Dr. Hunnicutt that he undertake a series of experiments with a view of determining the matter definitely. Observing aseptic precautions in the strictest manner, Dr. Hunnicutt has made a large number of experiments on dogs, and we are able to report that in none of the thyroids thus far examined has there been the slightest evidence of hyperplasia. The average time allowed to elapse between the removal of the first and second lobes was fifty-five days, the shortest interval being thirty and the longest eighty-one days.

That, nevertheless, there is such a thing as true compensatory hyperplasia of the thyroid gland is proved, I think, by my experiments in transplantation of the parathyroid glandules; which were conducted with the strictest aseptic precautions. Thus when both thyroid lobes and the four parathyroid glandules have been removed and only a film of thyroid transplanted with one parathyroid body, this film hypertrophies enormously, and on microscopic examination displays the typical changes of extreme hyperplasia. In one instance in which the graft was examined fifteen months after operation, the transplanted film had become as large as a good-sized pea.

If it should become a definitely established fact that true compensatory hyperplasia of the thyroid occurs only after the removal of a considerable part of this gland, and that infection or diet or some unknown factor has been responsible for most of the hypertrophies hitherto recorded, investigations are then made possible which could not be undertaken to any purpose if hyperplasia might be expected to follow operative interference of almost any sort upon the thyroid lobe.[2]

Although expecting that in wounds which healed by first intention hyperplasia might not develop after excision of small portions of one thyroid lobe, it surprised me to find from this year's experiments that so much as one and a half lobes may be removed without appreciable effect upon the remainder of the gland, and for the moment my interest in the search for an explanation of the entire absence of any sign of hypertrophy in the experiments of the past winter is as keen as it was years ago to explain the invariable hypertrophy which followed almost any sort of operative interference with the glandula thyroidea. Dr. Marine, replying a few days ago from Vienna to a letter in which I asked for his opinion, writes: "I am anxious to know whether you used iodine in the sterilization of the skin. This, as you know, inhibits to a marked degree compensatory hyperplasia following partial removal just as it does any physiological outgrowth. After trying all sorts of ways to check your 1888-1889 results we always got exactly what you then reported, and I shall have to have very conclusive evidence before being convinced that your results obtained in 1888 could be explained on the bases of wound infection." . . . "You have doubtless controlled the diet as a factor in compensatory hyperplasia."

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[2] In 5 unvaccinated dogs operated upon without precautions and whose wounds were left open, there was, greatly to my surprise, not the slightest indication of hypertrophy of the remaining lobe after thirty days.

In most of our experiments the skin has been disinfected with iodine, but in numerous instances it was not.

In 1888 our dogs were fed chiefly on raw meat, whereas during the past year their food has consisted almost exclusively of corn bread and cooked lungs of beeves. From the observations of David Marine, Reid Hunt, Chalmers Watson and others, which bear on this subject, it seems not unlikely that in the diet may be found the solution of the problem.

Should we find that, as a rule, three-fourths or more of the entire gland must be removed before the hyperplasic changes develop, this will be additional evidence to strengthen the belief that the thyroid gland is normally in a state of relative inactivity, and that it is an organ with great reserve power, capable of responding promptly, almost instantly, to certain stimuli.

Of particular interest in this connection are the experiments, just published, of Dr. Reich and Prof. Blauel, of Vienna. They find that in rats, whose thyroids normally have cuboidal epithelium, compression of the trachea is followed by flattening of this epithelium, to an extreme degree. If the oxygen-deprivation induced by the obturation of the trachea should prove to be the cause of the regressive or hypotrophic changes, might we expect to find that the colloid goitres which produce a great degree of tracheal stenosis are less likely to become Basedowified than those which are not accompanied by symptoms of suffocation?

Among the queries which present themselves at the moment are the following:

1. Must a deficiency be created for the successful grafting of ductless glands? Biedl claims to have successfully transplanted two parathyroid homografts in a dog which had not been deprived of any of its parathyroids. To justify his position, he states that all depends upon how long a transplant must live in order to be called a successful one. It seems to be an unchallenged proposition that a transplant cannot live unless it is functioning. But what is meant by functioning? Are tissues growing *in vitro* performing a function? Are the spirals of elastic tissue which we wind about the aorta functioning for a time? For about two months these spiral bands seem to live and continue to constrict the artery, but in six months they are almost absorbed.

2. What proportion of both thyroid lobes is it necessary to remove in order to produce hyperplasia of the remainder? The removal of one and one-half lobes has not been followed by hypertrophy in our experiments of this year.

3. Can a graft live without showing the hyperplastic picture? In other words, will a graft be absorbed unless the deficiency created is so great that hyperplasia must develop? Should the fact that a surviving graft retains the normal structure be taken as evidence that it will be absorbed (that its life will be short of duration)? And could a graft with such dubious existence be stimulated to hypertrophy and to prolonged life by the introduction of conditions which might demand of the thyroid increased function?

If we are still in doubt as to the cause of the hypertrophy of the thyroid glands in our experiments of twenty-five years ago, and are unable to explain its entire absence in our dogs of this past winter, after making scores of experiments to determine the effect of the removal of part of one gland on the remainder of the same organ, how infinitely greater are the difficulties incident to the explanation of the effects upon ductless glands other than the one surgically attacked.

Hypertrophy or enlargement of the hypophysis, for example, described by many authors as following thyroidectomy, has been observed in various parts of the gland: in the anterior lobe, in the pars intermedia, and even in the pars nervosa. There are conflicting views as to the changes which take place both as to situation and histological detail. By most investigators the formation of colloid is emphasized, and this has been interpreted by several as signifying a taking on by the hypophysis of the function of the thyroid; the colloid in the former replacing this substance lost in consequence of the thyroidectomy.

But when experimental hyperplasia of the thyroid takes place, the colloid, instead of being increased in the remaining hypertrophied lobe, is diminished or disappears altogether; and this being the case, it would seem strange that, after thyroidectomy, it should appear in compensating fashion in the pituitary gland. We think of the normal thyroid, with its large follicles filled with colloid, relatively dense and deeply staining, as being in a state of comparative inactivity or rest; and the histological changes which have been stimulated in one gland by the removal of another have usually been considered as representing hyperactivity of this gland. But to me it appears unlikely that the colloid in the hypophysis which it is assumed makes its appearance in response to thyroid deficiency should signify hyperactivity of that organ, when the same colloid in the thyroid is found in abundance only in the comparatively inactive period of this gland.

It seems to be a natural inference that the loss of one gland of internal secretion should lead to the compensatory hypertrophy of another; and should colloid make its appearance in the eagerly observed unaccustomed places after the removal of a gland which normally is composed chiefly of colloid, the evidence for the compensatory nature of the change would seem to be so complete as to make further substantiation unnecessary. But I am quite sure that the evidence for the current view is not conclusive.

Is it not more probable that the elimination of the function of the thyroid may lessen, directly or indirectly, the demands on other of the ductless glands, and that the colloid changes noted in the hypophysis and parathyroids after thyroidectomy may signify hypo- and not hyperactivity of these organs?

A contribution by Kummer,[3] of Geneva, to the study of postoperative tetany, presented at the Twenty-fifth Session of the Congrés Française de Chirurgie, Paris, 1912, is worthy of unusual consideration. A women, completely deprived of the cervical thyroids and parathyroids, was kept alive for two years.

The autopsy was made by Prof. Askanzy,[4] who found in the hypophysis changes which seem to be identical with those described by William G. MacCallum[5] as having been present in the hypophysis of one of my dogs fifteen months after the removal of both thyroid lobes and of the four parathyroids. This dog, kept alive for this long period by a parathyroid autograft only 14 mm. in diameter, died of tetany on the removal of the transplant.

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[3] Contribution à l'étude de la Tétanie postopératoire. Extrait des Comptes Rendus du 25° Congrès de l'association Francaise de Chir., 1912.

[4] Quotation from Askanzy: "*Hypophyse.* Les cellules chromophiles ou éosinophiles sont très abondamment développées, d'une richesse même extraordinaire. Par contre il n'y a pas d'augmentation de substance colloide dans les amas cellulaires de l'hypophyse, comme cela se voit dans les hypophyses chez les myxoedémateux. C'est seulement près de la partie nerveuse d'ailleurs intacte, dans la zone intermédiare soit médullaire, que l'on constate quelques follicules à substance colloide conformément à l'aspect ordinaire."

[5] Quotation from MacCallum: "The hypophysis shows rather distinct alterations. The pars nervosa is practically surrounded in the section by the pars intermedia which is perhaps slightly thickened and contains one or two alveoli full of colloid. The pars anterior is in part very deeply stained with eosin, but one portion, and that the major part, is sharply marked off from this eosin-stained tissue by its lilac color. It contains only a few of the bright staining cells, but for the most part is made up of swollen, faintly granular, pale stained cells. These resemble very closely the section obtained by Dr. Homans after injecting pilocarpin. The cleft in the glandular part of the hypophysis is here seen to open into the subarachnoid space." Halsted, Jour. of Exp. Med., 1912, xv, No. 3, 209.

Rarely again should there be an opportunity to study on the human subject the effects, after two years, of the complete removal of the thyroid and parathyroid glands.

We have never observed hypertrophy of the transplanted parathyroids even when total thyroidectomy and total parathyroidectomy have been done. I am not prepared, at present, to report the results of operations to determine the effect, if any, upon the thyroid of excision of the parathyroids; but I am not quite willing to accept as proved the observations of others who claim that after thyroid lobectomy the parathyroids are stimulated to compensatory hypertrophy, forming follicles containing colloid. *Why should the excision of an amount of thyroid insufficient to bring about thyroid hyperplasia cause compensatory hyperplasia of the parathyroid glandules? And, granted that changes may have occurred in the glandules after thyroid lobectomy, should these consist in the formation of a colloid equivalent to the colloid of the thyroid alveolus if the thyroid-colloid disappears in cases of definite privation and if the accumulation of colloid seems to signify a state of normal or hypo- rather than of hyperactivity?*

Furthermore, if hypertrophy of the parathyroids really occurs after thyroidectomy, might it not be due to the unintentional destruction of some of the parathyroids, or even to infection of the wound? I have never observed hypertrophy of a transplanted parathyroid gland. The tendency of these grafts, in my experience, is always to atrophy.

An enormous amount of experimentation must be done before these questions, which are in no sense remote, can be answered. There are hundreds of eager workers in this fascinating field at present who may add immensely to the confusion, before, from the chaos, order eventually can emerge and the simple laws be established of which perhaps we are not even beginning to dream.

Hypertrophy of the thymus gland has frequently been observed in Graves' disease, and from our observations during the past ten or eleven years of a considerable number of such cases in which the greater part of both thyroid lobes has been removed, we think there is reason to believe that the thymus atrophies in consequence of the operation upon the thyroid. The lymphocytosis gradually disappears, and in none of the earlier cases which have presented themselves this past year for examination has the thymus been skiagraphically visible. It would seem, therefore, that the thymus may be activated by the thyroid.[6]

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[6] Support to this view is given by the results of the experiments of A. L. Tatum reported since the reading of this paper (*vid.* Jour. Exp. Med., June 1, 1913). Tatum finds that in rabbits the thymus atrophies after excision of the thyroid gland.